Childhood Immune Maturation and Allergy Development: Regulation by Maternal Immunity and Microbial Exposure

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Running head: Maternal immunity and childhood allergy

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Abstract

The increasing allergy prevalence in affluent countries may be caused by reduced microbial stimulation, resulting in an abnormal postnatal immune maturation. Most studies investigating the underlying mechanisms have focused on postnatal microbial exposure. Also the maternal microbial environment during pregnancy may program the immune development of the child, however. Prenatal environmental exposures may alter gene expression via epigenetic mechanisms, aiming to induce physiological adaptations to the anticipated postnatal environment, but potentially also increasing disease susceptibility in the offspring. Although the importance of fetal programming mostly has been studied in cardiovascular and metabolic disease, this hypothesis is also very attractive in the context of environmentally influenced immune-mediated diseases. This review focuses on how maternal immunity and microbial exposures regulate childhood immune and allergy development. Efficacious preventive measures, required to combat the allergy epidemic, may be identified by determining how the immune interaction between mother and child is influenced by microbial factors.

Key words

Fetal programming, allergy, immune regulation, epigenetics, microbial exposure
Introduction

Allergic diseases have become a major public health problem in affluent societies\textsuperscript{1,2}. Asthma is the most common chronic disease among children, with a major impact on both the physiological and psychological well-being of young children\textsuperscript{3}, as well as on socio-economic costs due to hospital admittance, treatment costs and parental sick leave\textsuperscript{4}. The allergy epidemic must be counteracted by research identifying successful preventive measures, which do not exist today.

The allergic march

Allergic diseases are characterized by inappropriate immune responses to innocuous foreign proteins, allergens. Atopy is defined as personal and/or familiar tendency to produce IgE antibodies to allergens, \textit{i.e.} become sensitized\textsuperscript{5}. The excessive Th2-like responses to allergens in atopic individuals include high production of IgE-inducing IL-4 and IL-13 and eosinophilia-enhancing IL-5 and IL-9\textsuperscript{6,7}. During the early phase of the IgE-mediated allergic reaction, allergen crosslinking of IgE antibodies on mast cells and basophils triggers release of inflammatory mediators\textsuperscript{7}. Cytotoxic mediators from eosinophils are important in the late phase reaction, and lead to chronic inflammation\textsuperscript{7}.

Atopic eczema, bronchial asthma, allergic rhinoconjunctivitis and immediate types of urticaria and food allergy all belong to the allergic diseases. The allergic march typically begins with the development of IgE antibodies to food allergens accompanied with symptoms of atopic eczema and food allergy\textsuperscript{8}. After sensitization during infancy, most children develop tolerance to food allergens\textsuperscript{8}. Later in childhood, inhalant allergen sensitization develops together with asthmatic symptoms, while onset of allergic rhinoconjunctivitis is usually seen from early school age\textsuperscript{8}.

Reduced microbial stimulation and the allergy epidemic
As changes in the genotype cannot explain the rapid increase in the allergy prevalence, loss of protective factors or appearance of risk factors in the environment may contribute to the increased prevalence of these diseases since the middle of the last century. A reduced microbial pressure, resulting in insufficient induction of T cells with regulatory and/or Th1-like properties to counteract allergy-inducing Th2 response, may underlie the allergy epidemic 9-13. Most studies investigating the underlying mechanisms have focused on postnatal microbial exposure 14-18.

An increasing body of evidence from studies of others and us suggests that the maternal microbial environment during pregnancy can program the immune development of the child, however 13, 19, 20. Thus, experimental murine models demonstrate that maternal treatment with lipopolysaccharide 21-23 or the commensal *Acinetobacter lwoffii* 24 during gestation attenuates allergic sensitization and airway inflammation in the offspring. Also, epidemiological studies indicate that maternal farm environment exposure during pregnancy protects against allergic sensitization and disease, whereas exposures during infancy alone have weaker or no effect at all 13, 25, 26. Continued enhanced postnatal microbial exposure may be required for optimal allergy protection, however 26. Furthermore, in human allergy intervention studies, probiotic supplementation to the mother during pregnancy, as well as to her baby postnatally, may be important for preventive effects 27, 28. Thus, a preventive effect on atopic eczema has primarily been demonstrated in studies by us and others where probiotics were given both pre- and postnatally 19, 29-33, whereas two studies with postnatal supplementation only failed to prevent allergic disease 34, 35. Prenatal probiotic supplementation was not given until 36 weeks of gestation in any of the studies, however 19, 29-33. If prenatal microbial exposure is vital for the preventive effect, starting supplementation already from the second
trimester of pregnancy, when circulating fetal T cells have developed, may have a more powerful preventive effect on allergy development.

**Epigenetic regulation**

Regulation by epigenetic mechanisms, heritable changes in gene expression occurring without alterations in the DNA sequences, a kind of cellular memory, may play a major role in prenatal immune programming. Epigenetic modifications determine the degree of DNA compaction and accessibility for gene transcription, thus resulting in changes in gene expression that are subsequently passed to somatic daughter cells during mitosis. The main processes modulating DNA accessibility to establish epigenetic memory occur via posttranslational histone modifications and methylation of DNA CpG dinucleotides. DNA methylation, associated with transcriptional repression, is more rigid than histone modifications, with DNA methyltransferases conferring covalent methyl modifications to evolutionary conserved regulatory gene elements, CpG islands. The methylation pattern is thus preserved with high fidelity through cell divisions, assuring preservation of cellular inheritance.

**Epigenetic regulation of childhood immune development**

Prenatal environmental exposures may alter gene expression via epigenetic mechanisms, aiming to induce physiological adaptations to the anticipated postnatal environment, but potentially also increasing disease susceptibility in the offspring. This "Developmental Origins of Health and Disease" hypothesis was originally proposed by David Barker. Although the importance of fetal programming mostly has been studied in cardiovascular and metabolic disease, this hypothesis is also very attractive in the context of environmentally influenced immune-mediated diseases. The maternal microbial environment during pregnancy may program the immune development of the child, via epigenetic mechanisms, regulating appropriate maturation of innate immunity.
and T helper and regulatory responses. Th1, Th2 and Th17 differentiation is under epigenetic control, and human T regulatory cell commitment requires demethylation of the FOXP3 promoter.

The role of maternal microbial exposure and immune regulation in childhood allergy development

Epigenetically regulated childhood immune development by maternal microbial exposure is likely induced via changes in maternal immune regulation, as there is a close immunological interaction between the mother and her offspring during pregnancy. The placenta allows a cross-talk between maternal stimuli, possibly induced via microbial stimulation of maternal Toll-like receptors, and fetal responses. As fetal T cells have developed during the second trimester of gestation, maternal signals may then direct the immune cell lineage commitment of the offspring during a critical developmental period when the epigenetic program is highly susceptible to environmental influences. During pregnancy, the fetal-maternal interface is characterized by high levels of Th2-like cytokines and enrichment of T regulatory cells, most likely functioning to divert the maternal immune response away from damaging Th1-mediated immunity. The association of cord blood IgE levels and neonatal IFN-γ production with maternal but not paternal atopic heredity may depend on an even stronger Th2-deviation in atopic than non-atopic pregnant women. As the cytokine milieu shapes the T helper differentiation, particularly during naïve as compared to established responses, the neonatal immune system is Th2-skewed. The Th2 cytokine locus of in murine neonatal CD4+ T cells is poised epigenetically for rapid and robust production of IL-4 and IL-13. We have shown an even more marked neonatal Th2-skewing in infants later developing allergic disease, possibly due to prenatal epigenetic effects via
maternal immune regulation that may be possible to redress by enhanced microbial exposure, e.g. via probiotic supplementation, during pregnancy. The Th2-bias of the new-born should then develop toward a more balanced immune phenotype, including maturation of Th1-like responses and appropriate development of regulatory T cell responses. In farm studies, contact with multiple animal species during pregnancy is positively correlated to Treg cell function and IFN-γ production at birth and with innate immune receptor expression at birth and during childhood. A failure of Th2-silencing during maturation of the immune system may underlie development of Th2-mediated allergic disease. Appropriate microbial stimulation, both pre- and postnatally, may be required to avoid this pathophysiological process.

In this respect, the gut microbiota is quantitatively the most important source of microbial stimulation and may provide a primary signal for the maturation of a balanced postnatal innate and adaptive immune system. It is likely that our immune system has evolved as much to manage and exploit beneficial microbes as to fend off pathogens. The gut microbiota differs during the first months of life in children who later do or do not develop allergic disease, and the diversity of the microbiota may play an important role in regulating allergy and mucosal immune development. To what extent the maternal gut microbiota composition influences that of her offspring is not yet fully clear. Differences in microbiota composition depending on delivery mode do indicate a mother-child transmission of microbiota during vaginal delivery. Due to the vast complexity of the gut microbiota, more detailed, basic microbial ecology studies, now made possible by advances in DNA sequencing technologies, in clinically and immunologically well-characterized children and their mothers are needed, however. Also, how the maternal gut microbiota impacts the development of the microbiota of the child, in addition to the effects on immune maturation during infancy, needs further investigation.
Conclusion

The maternal microbial environment during pregnancy may program the immune development of the child. Prenatal environmental exposures may alter gene expression via epigenetic mechanisms, aiming to induce physiological adaptations to the anticipated postnatal environment, but potentially also increasing disease susceptibility in the offspring. Efficacious preventive measures, required to combat the allergy epidemic, may be identified by determining how the immune interaction between mother and child is influenced by microbial factors.

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